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ORIGINAL ARTICLE

Endoscopic Resection for Undifferentiated Early Gastric Cancer: Focusing on Histologic Discrepancies Between Forceps Biopsy-Based and Endoscopic Resection Specimen-Based Diagnosis

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Abstract
Background Before endoscopic resection (ER), a considerable number of undifferentiated early gastric cancer (UD-EGC) cases were initially diagnosed as atypical glands, dysplasia, or differentiated EGC (D-EGC) based on forceps biopsy specimens. As UD-EGC carries a high risk of resection margin involvement, identifying the predictive factors for UD-EGC cases with histologic discrepancy (HD) is of clinical importance.
Aims To investigate the outcomes of ER for UD-EGC and to identify the predictive factors for UD-EGC with HD.
Methods Among 2,194 EGC lesions treated by ER, 59 lesions were finally diagnosed as UD-EGC and 50 UD-EGC cases showed HD. The demographic and endoscopic characteristics were compared between D-EGC and UD-EGC with HD, and the predictive factors for the latter were investigated among cases of forceps biopsy-based diagnosis of atypical glands, dysplasia, or D-EGC.
Results UD-EGC showed significantly higher rate of lateral margin involvement compared to D-EGC (18.6 vs. 3.4 %). Among the UD-EGC cases meeting the expanded criteria and not involving additional surgery, no local or extragastric tumor recurrence was observed during the median follow-up of 27.5 months. Multivariate analysis demonstrated that age (≤60 years), female gender, gastric body, flat or depressed type, and tumor size (>2 cm) were independent predictive factors for UD-EGC with HD among cases of forceps biopsy-based diagnosis of atypical glands, dysplasia, or D-EGC.
Conclusions For lesions with predictive factors for UD-EGC with HD, a circumferential mapping biopsy before ER or wide marking during ER could be considered to avoid the potential risk of incomplete resection.

Keywords Undifferentiated cancer · Histologic discrepancy · Endoscopic resection · Clinical outcome

Introduction

Gastric cancer is the most common malignancy in Korea [1]. The proportion of early gastric cancer (EGC) has been increasing in Korea since a national mass screening program for gastric cancer was introduced in 1999 [2]. Although surgery is considered to be a standard treatment for EGC, endoscopic resection (ER) is now gaining wide acceptance because it can preserve the stomach and consequently improve quality of life as compared to radical gastrectomy. For selected cases of differentiated EGC (D-EGC), ER including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) is currently recognized as a standard treatment [3–6]. Contrary to D-EGC, the application of ER for undifferentiated EGC

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(UD-EGC) is still limited for fear of lymph node metastasis. However, several recent studies have reported that there is a negligible risk of lymph node metastasis in intramucosal UD-EGCs measuring less than 2 cm in size without ulcerations or lymphovascular invasion [7–10]. Based on these results, Gotoda et al. [9] proposed expanded criteria for ER including selected cases of UD-EGC. Recent studies have shown that the long-term outcomes after ER are favorable for UD-EGC meeting the expanded criteria [11, 12]. However, when ER has been performed for UD-EGC, a high incomplete resection rate has been reported due to frequent tumor involvement of the resection margin. One of the major reasons for lateral resection margin involvement is the spread of intramucosal cancers beyond their gross margins [13]. Because of the high incomplete resection rate, a circumferential mapping biopsy around the lesion before ER or wide marking during ER is usually recommended in Korea and Japan when ER is attempted for the cases with initial forceps biopsy-based diagnosis of UD-EGC.

There can be discrepancies between the initial forceps biopsy-based diagnosis and the final diagnosis based on the ER specimen. The rate of histologic discrepancy (HD) in EGC ranges from 16.3 to 53.7 % [14–19], with a higher rate in UD-EGC than in D-EGC [15]. Before ER, the initial forceps biopsy-based diagnosis of both D-EGC and UD-EGC with HD could be atypical glands, low- or high-grade dysplasia, or D-EGC. As UD-EGC carries a high risk of resection margin involvement, predicting UD-EGC cases with HD is of clinical importance in improving the complete resection rate. If UD-EGC is clinically suspected even if the pathologic review of the forceps biopsy specimen reveals atypical glands, dysplasia, or D-EGC, a circumferential mapping biopsy around the lesion before ER or wide marking during ER could be useful strategies to increase the complete resection rate.

In the present study, we investigated the outcomes of ER for UD-EGC. In addition, we tried to identify the predictive factors for UD-EGC with HD among cases with forceps biopsy-based diagnosis of atypical glands, dysplasia, or D-EGC.

Methods

Patients

Among 2,194 patients who underwent ER for EGC at Samsung Medical Center from October 2002 to June 2011, a total of 59 patients who were finally diagnosed as UD-EGC were enrolled in this study. During the study period, all of the EMR and ESD procedures for EGC were performed by three experienced endoscopists (BHM, JHL, and JJK). Chromoendoscopy using indigo carmine was employed to define tumor size and abdominal computed tomography (CT) was performed to detect lymph node metastasis in all patients before ER. At our institution, the primary treatment option for UD-EGC is radical gastrectomy. ER is indicated for UD-EGC meeting the expanded criteria only when patients have a high surgical risk or refuse to undergo surgery. Of the 59 patients with UD-EGC, the initial pathologic diagnoses based on forceps biopsy specimen were D-EGC ($n = 39$), atypical glands ($n = 6$), HGD ($n = 3$), indefinite for dysplasia ($n = 2$), and UD-EGC ($n = 9$), respectively (Fig. 1). Therefore, in 50 patients (84.7 %, 50/59), there was a HD between the initial forceps biopsy and the ER specimen.

The EMR and ESD procedures of our institution have been described in detail elsewhere [20, 21]. In brief, ESD consists of three steps as follows: (1) injecting fluid into the submucosal layer to separate it from the proper muscle layer; (2) circumferential cutting of the mucosa surrounding the lesion; and (3) submucosal dissection of the connective tissue under the lesion using an electrosurgical knife. In the EMR procedure, a snare is used for resection instead of an electrosurgical knife. Circumferential cutting is performed in case of EMR-P and not in cases of strip biopsy, EMR-C, or EMR-L. All procedures were performed after informed consent was obtained. The study protocol was approved by the Institutional Review Board at Samsung Medical Center.

Histopathological Evaluation

All resected specimens were stretched, pinned to a polystyrene plate, and fixed in 10 % neutral buffered formalin for more than 12 h. After fixation, all tissue sections were stained with hematoxylin–eosin. All resected specimens were serially sectioned into 2-mm slices to assess the tumor involvement of the lateral and/or vertical margins, the depth of invasion, and the presence of lymphovascular invasion.

Gastric cancer was classified as differentiated adenocarcinoma (well differentiated or moderate differentiated) or undifferentiated adenocarcinoma [poorly differentiated (PD) adenocarcinoma or signet ring cell (SRC) carcinoma]. HD was defined as cases with discrepancies between the initial forceps biopsy-based diagnosis and the final diagnosis based on the ER specimen. All EMR/ESD specimens were reviewed by two experienced gastrointestinal pathologists (KMK and CKP).

Size discrepancy was defined as a difference in the tumor size between the endoscopic estimation and the pathologic evaluation of the resected specimen. En bloc resection was defined as removal of the tumor as a single piece without fragmentation. Complete resection was

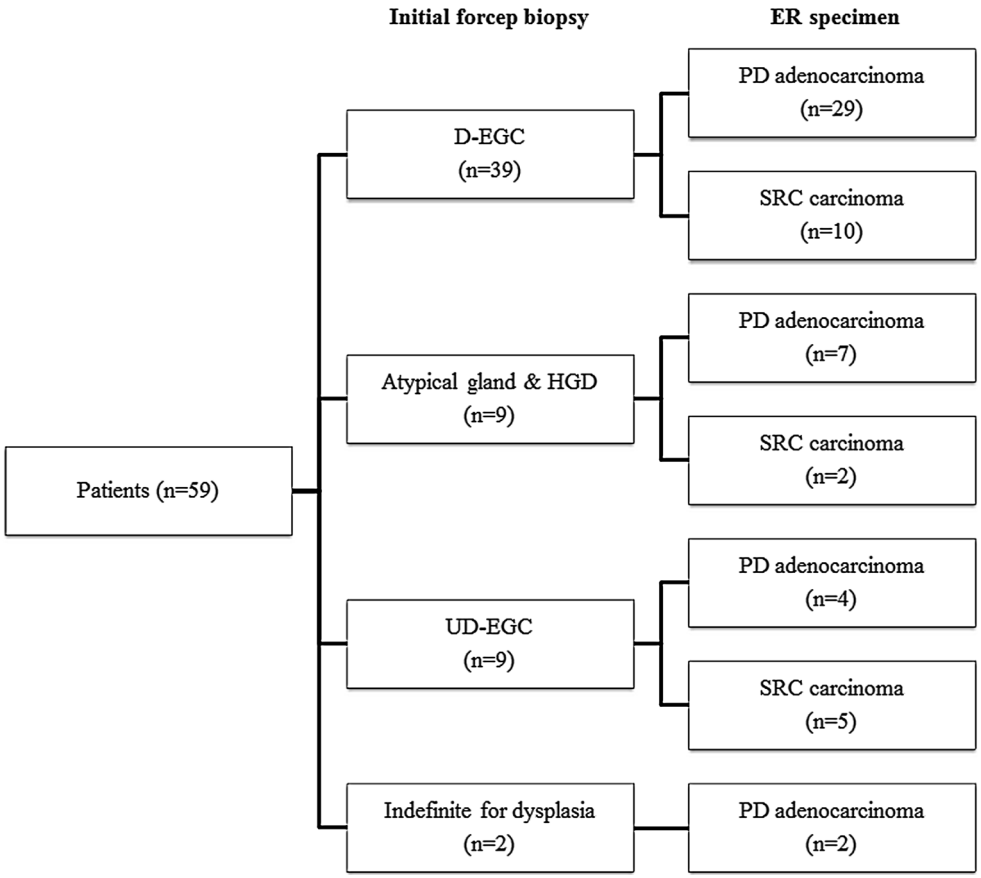

Fig. 1 Initial forceps biopsy-based diagnosis and final diagnosis based on the endoscopic resection specimens of 59 patients with undifferentiated early gastric cancer. *ER* endoscopic resection, *D-EGC* differentiated early gastric cancer, *PD adenocarcinoma* poorly differentiated adenocarcinoma, *SRC carcinoma* signet ring cell carcinoma, *HGD* high-grade dysplasia, *UD-EGC* undifferentiated early gastric cancer

defined as en bloc resection with tumor-free lateral and vertical resection margins. Curative resection was defined as UD-EGC undergoing complete resection and fulfilling the expanded criteria proposed by Gotoda et al. [9]. Local recurrence was defined as the detection of the cancer at the primary resection site in follow-up esophagogastroduodenoscopy (EGD) even though the pathologic review of the primary resection specimen had demonstrated no tumor on the lateral and vertical resection margins.

Follow-Up Strategy After ER

At our institution, EGD with a biopsy was scheduled 2 months after ESD to observe the healing of the artificial ulcer and detect the presence of any residual tumor. After the initial evaluation, EGD and abdominal CT were performed every 6 months for 3 years to detect recurrence. From the fourth to fifth year, patients underwent EGD and abdominal CT annually.

Statistical Analysis

The baseline characteristics of each case were compared using the χ^2 test or the Fisher's exact test for categorical data. The Mann–Whitney test was used for non-normally distributed continuous variables. The risk factors related to incomplete resection and HD were analyzed using logistic regression analysis. A p value <0.05 was considered statistically significant. All analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

Comparison of the Clinicopathologic Characteristics of UD-EGC and D-EGC

Among a total of 2,194 EGC patients who were treated by ER, 2,135 lesions (97.3 %) were finally diagnosed as D-EGC and 59 lesions (2.7 %) were finally diagnosed as UD-EGC (42 lesions were PD adenocarcinoma, and 17 were SRC carcinoma). The clinicopathologic characteristics of UD-EGC were compared with those of D-EGC (Table 1). Patients with UD-EGC had significantly larger tumor sizes and significantly more frequent size discrepancies between the endoscopic estimation and the pathologic evaluation as compared to D-EGC. UD-EGC also showed significantly higher rate of lateral margin involvement rate and consequently significantly lower rate

Table 1 Comparison of the clinicopathologic characteristics of differentiated and undifferentiated early gastric cancer

	D-EGC ($n = 2,135$)	UD-EGC ($n = 59$)	p value
Mean age (range), year	62.58 (26–88)	56.78 (22–84)	<0.001
Sex (male), *n* (%)	1,680 (78.7)	41 (69.5)	0.09
Location, *n* (%)			0.009
Upper	149 (7)	3 (5.1)	
Mid	385 (18.0)	25 (42.4)	
Lower	1,601 (75.0)	31 (52.5)	
Endoscopic finding, *n* (%)			0.045
Elevated	1,256 (58.8)	27 (45.8)	
Flat or depressed	879 (41.2)	32 (54.2)	
Tumor size, cm			<0.001
≤2 cm, *n* (%)	1,651 (77.3)	33 (55.9)	
>2 cm, *n* (%)	484 (22.7)	26 (44.1)	
Size discrepancy, cm			0.004
≤1 cm, *n* (%)	1,621 (77.0)	36 (61.0)	
>1 cm, *n* (%)	485 (23.0)	23 (39.0)	
Depth of invasion			0.071
Mucosa, *n* (%)	1,752 (82.1)	43 (72.9)	
Submucosa, *n* (%)	383 (17.9)	16 (27.1)	
Lymphovascular invasion, *n* (%)	138 (6.5)	9 (15.3)	0.008
Lateral margin involvement, *n* (%)	73 (3.4)	11 (18.6)	<0.001
Vertical margin involvement, *n* (%)	51 (2.4)	2 (3.4)	0.297
Complication			
Bleeding, *n* (%)	86 (4.0)	6 (10.2)	0.035
Perforation, *n* (%)	69 (3.2)	5 (8.5)	0.028
En bloc resection, *n* (%)	2,022 (94.7)	56 (94.9)	ns
Complete resection, n (%)	1,925 (90.2)	43 (72.9)	<0.001

D-EGC differentiated early gastric cancer, *UD-EGC* undifferentiated early gastric cancer

Table 2 Comparison of the clinicopathologic characteristics of poorly differentiated adenocarcinoma and signet ring cell carcinoma

	PD adenocarcinoma ($n = 42$)	SRC carcinoma ($n = 17$)	p value
Mean age (range), year	59.81 (39–84)	49.29 (22–82)	0.003
Sex (male), *n* (%)	32 (76.2)	9 (52.9)	0.079
Location, *n* (%)			0.654
Upper	3 (7.1)	0	
Mid	17 (40.5)	9 (52.9)	
Lower	22 (52.4)	8 (47.1)	
Endoscopic finding			0.899
Elevated	19 (45.2)	8 (47.1)	
Flat or depressed	23 (54.8)	9 (52.9)	
Tumor size, cm			0.403
≤2 cm, *n* (%)	25 (59.5)	8 (47.1)	
>2 cm, *n* (%)	17 (40.5)	9 (52.9)	
Size discrepancy, cm			0.047
≤1 cm, *n* (%)	29 (69.0)	7 (41.2)	
>1 cm, *n* (%)	13 (31.0)	10 (58.8)	
Depth of invasion, *n* (%)			0.091
Mucosa	28 (64.3)	15 (88.2)	
Submucosa	14 (33.3)	2 (11.8)	
Lymphovascular invasion, *n* (%)	7 (16.7)	2 (11.8)	ns
Lateral margin involvement, *n* (%)	6 (14.3)	5 (29.4)	0.551
Vertical margin involvement, *n* (%)	2 (4.8)	0	ns
Complication			
Bleeding, *n* (%)	5 (11.9)	1 (5.9)	0.662
Perforation, *n* (%)	4 (9.5)	1 (5.9)	ns
En bloc resection	40 (95.2)	16 (94.1)	ns
Complete resection	32 (76.2)	11 (64.7)	0.519

PD poorly differentiated, *SRC* signet ring cell

of complete resection as compared to D-EGC. The rates of complication including bleeding and perforation were higher in UD-EGC than in D-EGC.

Comparison of the Clinicopathologic Characteristics of PD Adenocarcinoma and SRC Carcinoma

In Table 2, we compared the clinicopathologic characteristics of PD adenocarcinoma and SRC carcinoma treated by ER. The mean age in SRC carcinoma was younger than that in PD adenocarcinoma. The mean tumor size was 1.98 ± 1.08 cm in PD adenocarcinoma and 2.32 ± 1.39 cm in SRC carcinoma. The submucosal invasion rates of PD adenocarcinoma and SRC carcinoma were 33.3 and 11.8 %, respectively. Significant size discrepancies between the endoscopic estimation and the pathologic evaluation were more frequently observed in SRC carcinoma than in PD adenocarcinoma. The lateral margin involvement rates of SRC carcinoma and PD adenocarcinoma were 29.4 and 14.3 %, respectively, although the difference between the two groups did not reach statistical significance. The en bloc resection rates and complete resection rates were comparable between the two groups.

Clinical Course of Patients with UD-EGC Undergoing ER

Figure 2 shows the clinical course of 59 patients with UD-EGC treated by ER. Among the 23 UD-EGC patients who met the expanded criteria for ER, none showed positive

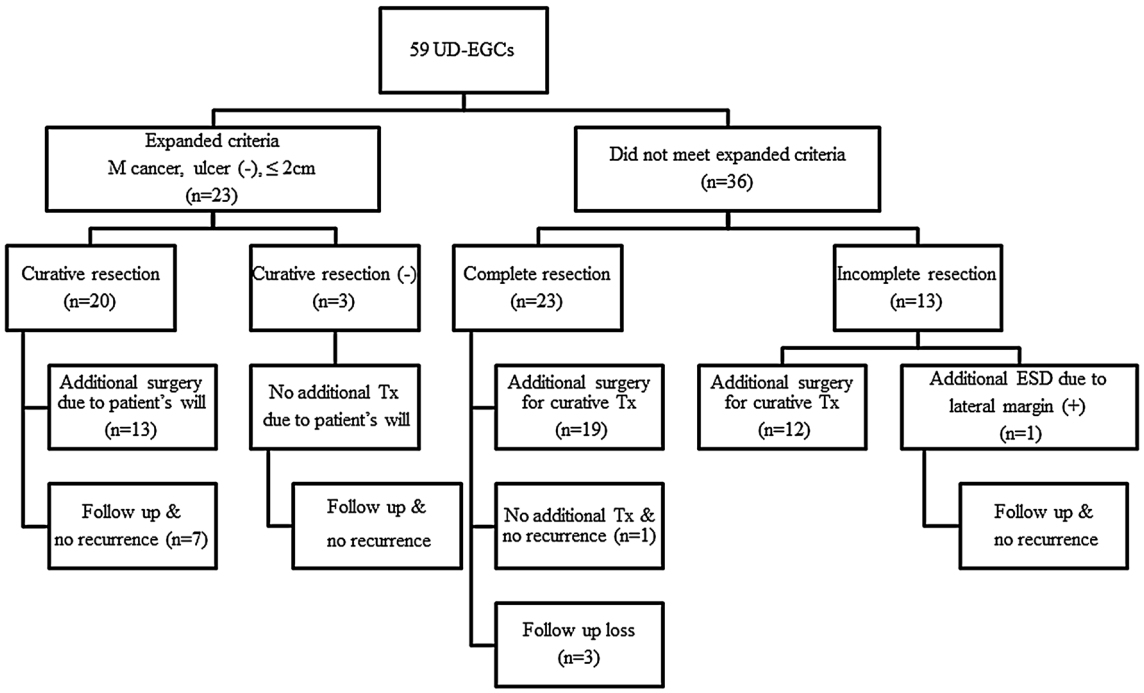

Fig. 2 Clinical course of 59 patients with undifferentiated early gastric cancer treated by endoscopic resection. *UD-EGC* undifferentiated early gastric cancer, *M* mucosal, *Tx* treatment, *ER* endoscopic resection

resection margins. Curative resections were achieved in 20 patients treated by ER. However, as the primary treatment option for UD-EGC at our institution is radical gastrectomy, surgery was recommended to patients even though they underwent curative ER. Therefore, 13 patients who underwent curative ER received additional radical gastrectomy. No lymph node metastasis was found in the surgical specimens in any of these patients. Among the 10 patients meeting the expanded criteria who did not undergo additional surgery, no local or extragastric tumor recurrence was observed during the median follow-up of 27.5 months (range 8–109 months). Among the 36 UD-EGC patients who did not meet the expanded criteria for ER, 31 patients underwent additional surgery. No lymph node metastasis was observed in the surgical specimens of these patients.

Risk Factors Associated with Incomplete Resection of UD-EGC

The demographic and endoscopic factors associated with the incomplete resection of UD-EGC were analyzed using univariate test (Table 3). All factors included in the analysis could be assessed before performing ER. Only tumor size (>2 cm) showed significant association with the incomplete resection of UD-EGC. No significant difference was found in the age, gender, tumor location, endoscopic

Table 3 Univariate analysis of the risk factors associated with incomplete resection of undifferentiated early gastric cancer

	Complete resection ($n = 43$)	Incomplete resection ($n = 16$)	p value
Age (year), *n* (%)			0.470
≤60	26 (60.5)	8 (50.0)	
>60	17 (39.5)	8 (50.0)	
Sex, *n* (%)			0.940
Male	30 (69.8)	11 (68.8)	
Female	13 (30.2)	5 (31.2)	
Location, *n* (%)			0.158
Antrum	25 (58.1)	6 (37.5)	
Body	18 (41.9)	10 (62.5)	
Endoscopic finding, *n* (%)			0.690
Elevated	19 (44.2)	8 (50.0)	
Flat or depressed	24 (55.8)	8 (50.0)	
Tumor size, cm			0.020
≤2 cm, *n* (%)	28 (65.1)	5 (31.3)	
>2 cm, *n* (%)	15 (34.9)	11(68.8)	
Histologic type, *n* (%)			0.369
PD adenocarcinoma	32 (74.4)	10 (62.5)	
SRC carcinoma	11 (25.6)	6 (37.5)	

PD poorly differentiated, *SRC* signet ring cell

Table 4 Multivariate analysis of the risk factors associated with incomplete resection of undifferentiated early gastric cancer

Variables	Odd ratio	95 % CI	*p* value
Age (≤60 vs. >60)	0.846	0.194–3.691	0.829
Location (antrum vs. body)	2.450	0.695–8.637	0.163
Endoscopic finding (elevated vs. flat or depressed)	0.575	0.156–2.122	0.406
Tumor size (≤2 cm vs. >2 cm)	4.291	1.176–15.656	0.027
Histologic type (PD adenocarcinoma vs. SRC carcinoma)	1.618	0.404–6.481	0.497

CI confidence interval, *PD* poorly differentiated, *SRC* signet ring cell

Table 5 Comparison of the demographic and endoscopic factors of differentiated early gastric cancer and undifferentiated early gastric cancer with histologic discrepancies

	D-EGC ($n = 2,135$)	UD-EGC with HD ($n = 50$)	*p* value
Age (year)			0.032
≤60, *n* (%)	873 (40.9)	28 (56.0)	
>60, *n* (%)	1,262 (59.1)	22 (44.0)	
Sex, *n* (%)			0.069
Male	1,680 (78.7)	34 (68.0)	
Female	455 (21.3)	16 (32.0)	
Location, *n* (%)			<0.001
Antrum	1,601 (75.0)	25 (50.0)	
Body	534 (25.0)	25 (50.0)	
Endoscopic finding, *n* (%)			0.017
Elevated	1,256 (58.8)	21 (42.0)	
Flat or depressed	879 (41.2)	29 (58.0)	
Tumor size, cm			<0.001
≤2 cm, *n* (%)	1,651 (77.3)	28 (56.0)	
>2 cm, *n* (%)	484 (22.7)	22 (44.0)	

D-EGC differentiated early gastric cancer, *UD-EGC* undifferentiated early gastric cancer, *HD* histologic discrepancy

finding, or histologic type between complete and incomplete resection. Multivariate analysis demonstrated that the tumor size (>2 cm) was an independent risk factor for incomplete resection of UD-EGC (Table 4).

Predictive Factors for UD-EGC with HD

D-EGC and UD-EGC with HD share several initial forceps biopsy-based diagnosis before ER: atypical glands, low- or high-grade dysplasia, and D-EGC (Fig. 1). We tried to identify the predictive factors for UD-EGC with HD by comparing the demographic and endoscopic factors between UD-EGC with HD and D-EGC. In the univariate analysis, UD-EGC with HD was significantly more frequently associated with age (≤60 years), gastric body, flat or depressed type, and tumor size (>2 cm) as compared to D-EGC (Table 5). Multivariate analysis demonstrated that age (≤60 years), female gender, gastric body, flat or depressed type, and tumor size (>2 cm) were independent predictive factors for UD-EGC with HD among cases of forceps biopsy-based diagnosis of atypical glands, low- or high-grade dysplasia, or D-EGC (Table 6).

Table 6 Multivariate analysis of the risk factors associated with undifferentiated early gastric cancer with histologic discrepancies among cases with forceps biopsy-based diagnosis of atypical glands, low- or high-grade dysplasia, or differentiated early gastric cancer

Variables	Odd ratio	95 % CI	*p* value
Age (≤60 vs. >60)	0.545	0.307–0.971	0.039
Gender (male vs. female)	2.151	1.155–4.006	0.016
Location (antrum vs. body)	2.828	1.590–5.029	<0.001
Endoscopic finding (elevated vs. flat or depressed)	2.016	1.129–3.602	0.018
Tumor size (≤2 cm vs. >2 cm)	2.425	1.360–4.327	0.003

CI confidence interval

Discussion

With the accumulation of data on the long-term outcomes after ER for EGC, Japanese doctors have sought to expand the indications of ER. Based on data from a large surgical database, Gotoda et al. [11, 12] proposed expanded criteria for ER including selected cases of UD-EGC. Recent studies have shown that the long-term outcomes after ER are favorable for UD-EGC meeting the expanded criteria. However, when ER was performed for UD-EGC, the incomplete resection rate has been reported to be high, ranging from 15 to 45 %, due to the ambiguous tumor margins and consequently frequent tumor involvement of the resection margins [11, 19, 22]. In the present study, the incomplete resection rate in UD-EGC was 27.1 %, much higher than that in D-EGC. There are several plausible explanations for the ambiguous tumor margins and consequent large size discrepancies between the endoscopically estimated tumor size and the pathologically determined tumor size in cases of UD-EGC, especially in SRC carcinoma. It was reported that tubule neck dysplasia, a precursor lesion of SRC carcinoma, extended along the proliferative zone leaving normal ducts covering the superficial mucosa [23]. Therefore, the real size of the SRC carcinoma can be larger than the endoscopic estimation based on the gross finding. In the present study, large size discrepancies were significantly more frequently observed

in SRC carcinoma than in PD adenocarcinoma (58.8 vs. 31.0 %).

Given this high rate of incomplete ER for UD-EGC, identifying predictive factors for incomplete resection is required. For cases of UD-EGC with predictive factors for incomplete resection, a circumferential mapping biopsy around the lesion before ER or wide marking during ER could be useful strategies to increase the complete resection rate. A previous study demonstrated that large tumor size and the presence of ulceration were independent predictive factors for incomplete resection in UD-EGC cases [19]. Similarly, in the present study, large tumor size was identified as an independent predictor factor for incomplete ER in UD-EGC.

There can be discrepancies between the initial forceps biopsy-based diagnosis and the final diagnosis based on the ER specimen. This HD in EGC ranges from 16.3 to 53.7 % [14–19]. In the present study, 84.7 % of UD-EGC cases showed HD, a much higher rate than those reported in previous studies. This high rate of HD was due to the institutional treatment strategy for UD-EGC favoring surgical treatment. At Samsung Medical Center, the primary treatment option for UD-EGC is radical gastrectomy. Therefore, most cases of initial forceps biopsy-based diagnosis of UD-EGC are treated by surgery, not by ER. Cases of forceps biopsy-based diagnosis of UD-EGC are treated by ER only when patients have high surgical risk or refuse to undergo surgery. Therefore, the majority of UD-EGC cases treated by ER at our institution had an initial forceps biopsy-based diagnosis of atypical glands, low- or high-grade dysplasia, or D-EGC and were finally diagnosed as UD-EGC based on ER specimen, which consequently resulted in the high rate of HD. As UD-EGC carries a high risk of resection margin involvement, predicting UD-EGC cases with HD has clinical implications for improving the complete resection rate. To date, however, few efforts have been made to identify predictive factors for UD-EGC with HD among cases of forceps biopsy-based diagnosis of atypical glands, low- or high-grade dysplasia, or D-EGC. Takao et al. [15] argued that the presence of mixed histology with differentiated and undifferentiated types within the lesion was one of the key features indicative of HD, and these HD might be due to the heterogeneity of gastric cancer. However, the presence of mixed histology could be diagnosed only after reviewing the specimen obtained from ER and could not be used as a predictive factor before ER. In the present study, age ($\leq$60 years), female gender, gastric body, flat or depressed type, and tumor size (>2 cm) were identified as independent predictive factors for UD-EGC with HD among cases of forceps biopsy-based diagnosis of atypical glands, low- or high-grade dysplasia, or D-EGC. For cases with these predictive factors for UD-EGC with HD, a circumferential mapping biopsy around the lesion before ER or wide marking during ER could be considered, as UD-EGC carries a high risk of incomplete resection associated with resection margin involvement. Confocal endomicroscopy or magnifying endoscopy combined with narrow-band imaging could be another promising modality for increasing complete resection rate as these methods can be probably useful for an accurate estimation of tumor margins [24, 25].

Recently, the indications of ER have been expanded based on the accumulation of clinical experience. Three recent studies have reported that the 5-year survival rates of UD-EGC meeting the expanded criteria have ranged from 83 to 96.7 % [11, 26, 27]. These results are comparable to those of D-EGC meeting the conventional or expanded indications. The results from our study supported these favorable outcomes after ER for UD-EGC. Among the 10 patients who met the expanded criteria and did not undergo additional surgery, no local or extragastric tumor recurrence was observed during the median follow-up of 27.5 months. No lymph node metastasis was observed in the surgical specimen in any of the UD-EGC patients undergoing additional surgery after ER.

This study had several limitations. First, as this study was single-center retrospective study, there was potential for a selection bias. We tried to minimize the selection bias by including the consecutive patients identified from our large database on ER. Second, as the primary treatment option for UD-EGC at our institution is radical gastrectomy, data on UD-EGC without HD were limited and only 10 UD-EGC patients meeting the expanded criteria did not undergo additional surgery and were medically followed up after ER. Given these limitations, further large-scale prospective studies are necessary to confirm our results.

In conclusion, our results indicated that UD-EGC meeting the expanded criteria could be a feasible target for ER. In addition, age ($\leq$60 years), female gender, gastric body, flat or depressed type, and tumor size (>2 cm) were identified as independent predictive factors for UD-EGC with HD among cases of forceps biopsy-based diagnosis of atypical glands, low- or high-grade dysplasia, or D-EGC. For the cases with these predictive factors for UD-EGC with HD, a circumferential mapping biopsy around the lesion before ER or wide marking during ER could be considered to avoid the potential risk of incomplete resection associated with UD-EGC.

Conflict of interest None.

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